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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 08/948,393
Filing Date: October 10, 1997
Appellant(s): WAGNER ET AL.

William G. Gosz
For Appellant

EXAMINER'S ANSWER

This is response to appellant's Appeal Brief, filed 1/9/06, appealing from the Office Action mailed 5/3/05.

The text of those sections of Title 35 U.S. Code not included in this appeal can be found in a previous Office Action herein.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the Brief, filed 1/9/06.

(2) Related Appeals and Interferences

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief, filed 1/9/06.

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of the claims in the Brief is correct.

This Appeal involves claims 71, 81, 85, 87-89, 92 and 94-97.

(4) Status of Amendments

Appellant's statement concerning the status of amendments in the Brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the Brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

Appellant's statement of the grounds of rejection in the Brief is correct.

As noted by appellant, in Section II on page 6 of the Brief,

USSN 09/436,076, which formed the basis of the obviousness-type double patenting rejection, has been abandoned;

which, in turn, has rendered the previous provisional double patenting rejection moot.

(7) Claims

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(8) Evidence Relied Upon

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

A. Aberg et al., U.S. Patent No. 5,061,694.

B. Casscells et al., U.S. Patent No. 5,308,622.

C. Coller et al., U.S. Patent No. 5,976,532

D. Cummings et al., U.S. Patent No. 5,464,778.

E. De Felice et al., Angiology 41: 1- 11, 1990.

F. Hinstridge et al. Drugs 42 (Suppl. 2): 8-2, 1991.

G. Larsen et al., U.S. Patent No. 5,840,679.

H. The Merck Manual of Diagnosis and Therapy, Sixteenth Edition, edited by Berkow et al., Merck Research Laboratories, Rahway, NJ 1992, see pages 409-413.

I. Sluiter et al., J. Cardiovascular Pharmacology 22 (Suppl. 4): S37-S44, 1993.

J. Tedder et al., U.S. Patent No. 5,834,425.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. § 103

Claims 71, 81, 85, 87-89, 92 and 94-97 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cummings et al. (U.S. Patent No. 5,464,778) in view of Larsen et al. (U.S. Patent No. 5,840,679), Tedder et al. (U.S. Patent No. 5,834,425), Coller et al. (U.S. Patent No. 5,976,532) and Sluiter et al. (J. Cardiovascular Pharmacology 22 (Suppl. 4): S37-S44, 1993) and further in view of Aberg et al. (U.S. Patent No. 5,061,694), Casscells et al. (U.S. Patent No. 5,308,622) and Hinstridge et al. (Drugs 42 (Suppl. 2): 8-2, 1991) and in further evidence of The Merck Manual of Diagnosis and Therapy, Sixteenth Edition (edited by Berkow et al., Merck Research Laboratories, Rahway, NJ 1992, pages 409-413) and De Felice et al. (Angiology 41: 1- 11, 1990).

For the record, the PSGL taught by Cummings et al. and Larsen et al. is the same PSGL-1 as that claimed. There has been no dispute on this issue during the prosecution of this application.

Cummings et al. teach the use of PSGL in the treatment of leukocyte adherence, inflammation and coagulation, including ischemia-reperfusion injury and atherosclerosis (see entire document, particularly column 18, paragraphs 5-8; columns 19-20, overlapping paragraph; and Claims). Cummings et al. teach the properties and the use of PSGL (column 9-18), including protein fragments thereof (e.g. column 20, paragraph 4) as well as the administration and monitoring according to one of ordinary skill in the art (column 21, paragraphs 2-3). The claimed functional limitations would be intrinsic or expected properties of the referenced methods of treating atherosclerosis with PSGL and fragments thereof.

Further, Cummings et al. teach that the therapeutic use that reduce leukocyte adherence in ischemic myocardium can significantly enhance the therapy efficacy of thrombolytic agents (see column 18, paragraph 7). Cummings et al. also teach that the treatment of chronic disorders may be attained by sustained administration of agents (e.g. see column 18, lines 50-53) as well as slow release formulations (e.g. see columns 20-21, overlapping paragraph).

Cummings et al. differs from the claimed invention by not disclosing "said agent being administered repeatedly in sequential doses or by the controlled release to the mammal over a period of months or years"; by not disclosing that treating or inhibiting "atherosclerosis by decreasing the formation or growth of plaque on arterial walls"; by not disclosing the various art known "vessel-corrective techniques" encompassed by the claimed invention; and by not disclosing the claimed dosages in the context of treating atherosclerosis.

With respect to PSGL-1 and in addition to the teachings of Cummings et al.,

Larsen et al. teach the use of PSGL (see entire document, including column 15, paragraph 3 – column 18; Examples and Claims), including fragments (e.g. columns 9-10) and fragments fused to carrier molecules such as immunoglobulins to increase avidity (e.g. chimeric forms of said PSGL (column 9-10, overlapping paragraph) to treat conditions characterized by P- or E-selectin mediated intercellular adhesion, such as myocardial infarction (columns 15-16, overlapping paragraph), including its combination with other pharmaceutical compositions, including anti-inflammatory and thrombolytic or anti-thrombotic agents (e.g. columns 16-18) (see entire document, including Summary of the Invention; Detailed Description of the Invention). Larsen et al. also teach various modes of administration and dosing (e.g. liposomes, pharmaceutical carriers), including combinations of agents would be provided in therapeutically effective amounts either serially or simultaneously sufficient for the needs of the patient, including the nature and severity of the condition being treated according to the attending physician (columns 16-18).

Therefore, Cummings et al. and Larsen et al. teach the art known use controlled release systems and teach the known use of combination therapy at the time the invention was made. The ordinary artisan would have provided therapeutic amounts of PSGL-1, fragments and chimeric constructs thereof to meet the severity of the condition and the needs of the patients, as taught by known and practiced by the ordinary artisan at the time the invention was made and taught by both Cummings et al. and Larsen et al. Therefore, the modes of administration and dosages encompassed by the claimed invention would have been met by the ordinary artisan at the time the invention was made to meet the severity of the condition and the needs of the patients, including the treatment of atherosclerosis with antagonistic PSGL-1. For example, see the teachings of modes of administration and dosages set forth in Larsen et al. on columns 16-18, including columns 17-18, overlapping paragraph.

Tedder et al. teach the art known generation and use of chimeric peptides combining ligand binding portions of selecting based inhibitory therapeutics, including those based upon P-selectin, with other molecules such as immunoglobulin to increase serum half-life or avidity of the therapeutic agent to block platelet or leukocyte-mediated inflammation (see entire document, including Use on columns 10-14). Similar to Cummings et al. and art known practice at the time the invention was made, Tedder et al. teach combination therapy with other therapeutic agents (see column 13, paragraph 1).

Coller et al. teach the art known vessel-corrective techniques at the time the invention was made in the treatment of cardiovascular disorders such as atherosclerosis and restenosis, including angioplasty, atherectomy and coronary bypass surgery (see Background of the Invention on column 1 and Utility of Platelet-specific Chimeric Immunoglobulin on columns 5-7). In teaching the use of an inhibitor of platelet aggregation and thrombus formation associated with such conditions, Coller et al. teach the art known use of combination therapy with other drugs such as thrombolytic agents and that the amounts administered before, along with or subsequent to treatment will depend on a variety of factors and clinical symptoms known to the ordinary artisan at the time the invention was made (see column 6, paragraphs 2-3).

Sluiter et al. has been provided to add further evidence that the ordinary artisan would have targeted the inhibition of P-selectin-mediated events in therapeutic strategies of inhibiting leukocyte adhesion receptors to alleviate tissue damage in cardiovascular diseases (see entire document, including Figure 1 and Table 1), including those patients suffering from heart attack, atherosclerosis and coronary restenosis (see Concluding Remarks on page S42).

Given the art known practice of combination therapy, as taught by Cummings et al., Larsen et al., Tedder et al. and Coller et al. as well as the art known practice of vessel-occlusive techniques to treat atherosclerosis, as taught by Coller et al., one of ordinary skill in the art would have been motivated to administer the PSGL-1 and fragments thereof, as taught by Cummings et al. in various vessel-occlusive techniques given its properties of inhibiting platelet-leukocyte interactions for various clinical applications, including atherosclerosis and ischemia, myocardial infarction and reperfusion injury, as taught by Cummings et al. with an expectation of success. Given the art known practice of modes of administrations and dosing depending on a variety of factors and clinical symptoms known to the ordinary artisan at the time the invention was made, as taught by Coller et al. In cardiovascular diseases, the claimed limitations were met or would have been obvious variants in meeting the needs of the patients in order to achieve a therapeutic effect depending on the symptom at the time the invention was made.

Also, as indicated previously with respect to atherosclerosis,

appellant's attempts to distinguish the instant claims from the prior art by amending the claims to recite:

A method for treating or inhibiting atherosclerosis "by decreasing the formation or growth of plaque on arterial walls"

was simply amending the claims to recite a description of certain underlying characteristics and elements of the same therapeutic endpoint of treating atherosclerosis.

For example as pointed out previously, while two main hypothesis (at least as of 1992) have been proposed to explain the pathogenesis of atherosclerosis, namely the lipid hypothesis and the chronic endothelial injury hypothesis, both of these hypotheses involved platelets and monocytes and associated growth factors.

See pages 409-413, particularly page 410, Atherosclerosis of The Merck Manual of Diagnosis and Therapy, Sixteenth Edition, edited by Berkow et al., Merck Research Laboratories, Rahway, NJ 1992.

In addition, De Felice et al. (Angiology 41: 1- 11, 1990) noted that:

"It has long since been known that mural thrombi contribute to the development and progression of atherosclerotic plaque."

See page 2, Secondary Prevention of Atherosclerosis and Thrombosis of De Felice et al.

De Felice et al. also noted that antiplatelet agents can influence the natural course of atherosclerosis.

See pages 2-3, Antiplatelet Agents of De Felice.

Also, Casscells et al. teach that atherosclerosis results from the development of an intimal lesion and the subsequent narrowing of the vessel lumen as well as the surgical procedures such as bypass surgery and balloon catherization in treating patients with artherosclerosis and as well as the association of restenosis in such patients (e.g. see column 2, paragraph 3). Here, Casscells et al. note preventing such reoccurrence in patients who have been treated atherosclerosis. Also, Casscells et al. teach that while a single dose may inhibit neointimal proliferation, administration over a period of time is preferred (e.g. see column 3, lines 46-48)

Also, as pointed out previously in response to appellant's arguments and recently amended claims, the following prior art provided the well known practice of providing treatment to meet the needs of the patient by the ordinary artisan and in the context of the treatment of atherosclerosis, this included prolonged treatment over a period of months or years.

Also, the following has been added to address appellant's arguments and recently amended claim limitation as follows:

"said agent being administered repeatedly in sequential doses or by the controlled release to the mammal over a period of months or years.

Aberg et al. also teach in the slowing the progress of atherosclerosis, including the reduction or eliminating atherosclerotic lesions (see entire document, particularly Summary of the Invention) that :

The formulations will be administered for prolonged periods, that is, for as long as it is necessary to treat the atherosclerosis. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed. A dosing period of at least one to two weeks are required to achieve minimal benefit.

See column 5, lines 55-61 of Aberg et al.

Hinstridge et al. provide An Overview of Therapeutic Interventions in Myocardial Infarction, Emphasis on Secondary Prevention, including treatment regimens for the prevention of further occlusion, infarction and death by preventing subsequent thrombosis and atherosclerosis (see page 9, column 1, paragraph 2) including the use of Antiplatelet Drugs that can be administered for 1-2 years (see pages 14-15, including page 14, column 2, paragraph 3) (see entire document).

Again, Casscells et al. teach that while a single dose may inhibit neointimal proliferation, administration over a period of time is preferred (e.g. see column 3, lines 46-48).

In addition to the long-term treatment with anti-platelet agents in the treatment of cardiovascular patients, including those with atherosclerosis, addressed above;

given the long term chronic nature of atherosclerosis, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide prolonged treatment of an appropriate inhibitor to meet the needs of the patient and the particular state of disease, which has been standard practice by the medical profession.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Rebuttal: Appellant's Arguments in the Brief.

Appellant's arguments in conjunction with the previous declaration under 37 C.F.R. 1.132 (Wagner II Declaration), have been fully considered but are not found convincing essentially for the reasons of record.

Appellant submits that Cummings et al. is directed to the treatment of acute inflammatory conditions, such as ischemia and reperfusion, rather than atherosclerosis and that the focal point of this reference is the prevention of leukocyte adherence to vascular endothelium.

Appellant further submits in conjunction with the Wagner (II) 132 Declaration that Cummings et al. is directed to the prevention of platelet activation in the circulatory systems, rather than the inhibition of endothelial cell binding which is an essential component of atherosclerosis and that the ordinary artisan would have had no reasonable expectation that PSGL-1 could be used to reduce plaque formation and further that a long term treatment regime would be required to achieve this result.

Appellant further asserts that Larsen et al. like Cummings et al. does not relate to the treatment of chronic conditions, such as atherosclerosis, but is instead directed to the treatment of inflammatory acute conditions.

However, in contrast to appellant's assertions in conjunction with the Wagner (II) 132 Declaration that Cummings et al. is limited to treating acute conditions or thrombus formation, Cummings et al. clearly teaches treating atherosclerosis and long term treatment with PSGL.

As appellant notes, Cummings et al. teach the following.

"Platelet-leukocyte interactions are believed to be important in atherosclerosis. Platelets might have a role in recruitment of monocytes into atherosclerotic plaques; the accumulation of monocytes is known to be one of the earliest detectable events during atherogenesis. Rupture of a fully developed plaque may not only lead to platelet deposition and activation and the promotion of thombus formation, but also the early recruitment of neutrophils to an area of ischemia."

See columns 19-20, overlapping paragraph of Cummings et al.

As appellant ignores, Cummings et al. also teach the following.

Since P-selectin has several functions related to leukocyte adherence, inflammation, tumor metastases and coagulation, clinically, compounds which interfere with binding of P-selectin and/or the other selectins, including E-selectin and L-selectin, can be used to modulate these responses. For example, **the glycoprotein ligand or components thereof can be used to inhibit leukocyte adhesion by competitively binding to P-selectin expressed on the surface of activated platelets or endothelial cells.** These therapies are useful in acute situations where effective, but transient, inhibition of leukocyte-mediated inflammation is desirable. In addition, **treatment of chronic disorders may be attained by sustained administration of agents**.

An inflammatory response may cause damage to the host if unchecked, because leukocyte release many toxic molecules that can damage normal tissues. These molecules include proteolytic enzymes and free radicals. **Examples of damage include injury from ischemia and reperfusion and atherosclerosis.**

See column 18, paragraphs 5-6 of Cummings et al.

Reperfusion injury is a major problem in clinical cardiology. **Therapeutic agents that reduce leukocyte adherence in ischemic myocardium can significantly enhance the therapeutic efficacy of thrombolytic agents.**

See column 18-19, overlapping paragraph of Cummings et al.

That applicant attempts to ignore the prior art teaching of treating atherosclerosis with soluble PSGL-1 but rather focuses on the teaching of acute thrombotic complications does not take away from the clear teaching of treating atherosclerosis with PSGL by the prior art, including the long term treatment of atherosclerotic patients and patients undergoing the same cardiovascular procedures as claimed and with the same or nearly the same complications, including the role of platelets, leukocytes and endothelial cells.

Also, as indicated previously and in contrast to appellant's assertions in the Brief,

the prior art is consistent with the claimed invention as well as the instant disclosure (see Background of the Invention of the instant specification) as well in teaching the importance of platelet-leukocyte-endothelial interactions in atherosclerosis (e.g. see columns 19-20, overlapping paragraph of Cummings et al.).

Therefore, in contrast to appelant's / Wagner's assertions,

the prior art not only teaches treating atherosclerosis but also teaches addressing the problems associated with atherosclerotic plaques and the role of leukocyte-platelet-endothelial interactions, including the role both platelets and leukocytes in atherosclerosis as well as the expression of P-selectin on endothelial cells and platelets and the applicability of inhibiting leukocyte-platelet-endothelial interactions generically and more specifically P-selectin interactions with soluble PSGL.

Also, while applicant focuses on differences in the intent of treating acute versus chronic conditions,

the prior art does teach treating the complications associated with both acute and chronic conditions, including patient populations under the same or nearly the same cardiovascular procedures for the same or nearly the same indications and complications with the same or nearly the same therapeutic endpoints of treating atherosclerotic patients, including those undergoing the claimed vessel corrective procedures by inhibiting PSGL:P-selectin interactions with soluble PSGL-1.

Again, appellant's attempts to limit the teaching of Cummings et al. to the role of platelets only in atherosclerosis in not supported by Cummings et al. as indicated above and is not consistent with appellant's own disclosure as filed (see Background of the Invention on pages 1-2 of the instant specification) nor with the various secondary teachings provided to address the scientific basis of atherosclerosis, wherein platelet, leukocytes and endothelial cells were known to play a role and were known to be targeted in therapeutic regimens at the time the invention was made.

Although appellant appears to dismiss the secondary references since they either do not teach the use of appellant's agent for the treatment of disease or they are addressing the scientific basis of atherosclerosis.

Even though Cummings et al. may not have described all of the vessel-corrective techniques currently claimed, Cummings et al. does teach treating atherosclerosis as well as other complications such as ischemia and reperfusion injury, which were known complications of patients undergoing the claimed vessel corrective techniques at the time the invention was made, as evidenced by combined references indicated above.

Also as pointed out above in the rejection, the various secondary references, including Coller et al., Sluiter et al, Casscells et al., The Merck Manual of Diagnosis and Therapy, Sixteenth Edition, De Felice et al. all are consistent with Cummings et al. that platelet, leukocytes and endothelial cells are involved in the multifactorial processes that are involved in thrombotic disorders, including atherosclerosis and the use of antithrombotic and antiplatelet agents, including thrombolytic drugs at the time the invention was made.

See the teachings of the secondary references above in the **Grounds of Rejection**.

The secondary references have been brought into the prosecution to address appellant's efforts to amend around the prior art teachings and to address appellant's arguments that platelets were not involved in atherosclerosis.

Again, appellant's arguments in the Brief are not consistent with Cummings et al. nor with the specification as filed and not with the prior art, as evidenced by Coller et al., Sluiter et al, The Merck Manual of Diagnosis and Therapy, Sixteenth Edition, De Felice et al.

However, by either ignoring or dismissing the teachings of the prior art, appellant has been attempting to limit the teachings of Cummings et al. and Larsen et al. to acute treatment only and not the combined teachings of the references, which are consistent with applicant's disclosure and claimed invention.

There was sufficient teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

With respect to the secondary references, appellant's attempt to simply dismiss the teachings of Sluiter et al. or Coller et al. because they do not teach PSGL-1 per se does not address their teachings of targeting P-selectin or platelets in the context of atherosclerosis or the vessel corrective techniques of the claimed invention.

See the teachings of Sluiter et al. and Coller et al. above in the **Grounds of Rejection**.

Also, as indicated previously, appellant's attempts to distinguish the instant claims from the prior art by amending the claims to recite:

A method for treating or inhibiting atherosclerosis "by decreasing the formation or growth of plaque on arterial walls" and

was simply amending the claims to recite a description of certain underlying characteristics and elements of the same therapeutic endpoint of treating atherosclerosis.

As noted in the Summary of the Invention of the instant specification, the methods of instant invention include administering an agent prior to formation of an atherosclerotic lesion as well as subsequent to formation of an atherosclerotic lesion, which can include preventing growth of an atherosclerotic lesion after a surgical procedure for preventing restenosis (see page 4, paragraphs 1-2 of the instant specification).

The prior art teachings are directed towards treating patients undergoing cardiovascular surgery as well as complications associated with ischemia-reperfusion injury and myocardial infarctions include those patients with atherosclerosis who undergo such procedures and, in turn, would be subject to treatment.

See the teachings of the same methods of inhibiting platelet-leukocyte / endothelial interactions for various clinical applications, including atherosclerosis and ischemia, myocardial infarction and reperfusion injury as well as cardiovascular disorders such as atherosclerosis, including angioplasty, atherectomy and coronary bypass surgery above in the **Grounds of Rejection**.

For example, Casscells et al. teach that atherosclerosis results from the development of an intimal lesion and the subsequent narrowing of the vessel lumen as well as the surgical procedures such as bypass surgery and balloon catherization in treating patients with artherosclerosis and as well as the association of restenosis in such patients (e.g. see column 2, paragraph 3). Here, Casscells et al. note preventing such reoccurrence in patients who have been treated atherosclerosis.

Appellant's attempts to detract from the clear teaching of treating atherosclerosis with the same PSGL-1 inhibitors as claimed has not been found convincing.

Also, under the broadest reasonable interpretation of the claimed methods, including appellant's own disclosure as filed,

the prior art teaches the same agent (PSGL-1) that inhibits interaction between P-selectin-mediated interactions of platelets, leukocytes and endothelial cells in the same or nearly the same dosages to meet the same needs of the patient and the particular condition, including atherosclerosis and long term treatment.

Appellant is reminded that the instant specification discloses that:

"Treating atherosclerosis is meant to include preventing, arresting, altering and reversing formation of atherosclerotic lesions."

See page 5, paragraph 2 of the instant specification.

The invention also includes a therapeutic agent in a dosage form and concentration suitable for treating or preventing atherosclerosis in a mammal in need of such treatment, the agent being effective to inhibit interaction between P-selectin and its ligand.

See page 16, paragraph 1 of the instant specification.

A therapeutically effective amount can be determined by one of ordinary skill in the art employing known factors of patient populations, agents and modes of administration using no more than routine experimentation.

See page 14, paragraph 4 – page 15, paragraph 1 of the instant specification.

In contrast to appellant's assertions concerning the lack of teaching of "said agent being administered repeatedly in sequential doses or by the controlled release to the mammal over a period of months or years",

the following has been noted.

Cummings et al. also teach that the treatment of chronic disorders may be attained by sustained administration of agents (e.g. see column 18, lines 50-53) as well as slow release formulations (e.g. see columns 20-21, overlapping paragraph).

Also, that treatment is dictated by the specific condition and will generally follow standard medical practices (e.g. see column 21, paragraph 1).

Aberg et al. teach in the slowing the progress of atherosclerosis, including the reduction or eliminating atherosclerotic lesions (see entire document, particularly Summary of the Invention) that :

The formulations will be administered for prolonged periods, that is, for as long as it is necessary to treat the atherosclerosis. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed. A dosing period of at least one to two weeks are required to achieve minimal benefit.

See column 5, lines 55-61.

Hinstridge et al. provide An Overview of Therapeutic Interventions in Myocardial Infarction, Empahsis on Secondary Prevention, including treatment regimens for the prevention of further occlusion, infarction and death by preventing subsequent thrombosis and atherosclerosis (see page 9, column 1, paragraph 2) including the use of Antiplatelet Drugs that can be administered for 1-2 years (see pages 14-15, including page 14, column 2, paragraph 3).

Casscells et al. teach that while a single dose may inhibit neointimal proliferation, administration over a period of time is preferred (e.g. see column 3, lines 46-48)

In addition to the long-term treatment with anti-platelet agents in the treatment of cardiovascular patients, including those with atherosclerosis, addressed above;

given the long term chronic nature of atherosclerosis, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide prolonged treatment of an appropriate inhibitor to meet the needs of the patient and the particular state of disease, which has been standard practice by the medical profession.

Given the art known practice of modes of administration and dosing depending on a variety of factors and clinical symptoms known to the ordinary artisan at the time the invention was made, as taught by Coller et al. in cardiovascular diseases, the claimed limitations were met or would have been obvious variants in meeting the needs of the patients in order to achieve a therapeutic effect depending on the symptom at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

With respect to applicant's arguments concerning the secondary references, once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to appellant's arguments that is nonanalogous art, it has been held that the prior art reference must either be in the filed of appellant's endeavor or, if not then be reasonably pertinent to the particular problem with which the applicant was concerned in to order to be relied upon as a basis for rejection of the claimed invention. See In re Oetiker 24 USPQ2d 1443 (Fed. Cir. 1992).

In this case, the prior art, including the secondary references, are all drawn to the same or similar methods of inhibiting platelet-leukocyte / endothelial interactions for various clinical applications, including atherosclerosis and ischemia, myocardial infarction and reperfusion injury as well as cardiovascular disorders such as atherosclerosis and restenosis, including angioplasty, atherectomy and coronary bypass surgery.

Given the art known practice of combination therapy, as taught by the prior art as well as the art known practice of vessel-occlusive techniques to treat atherosclerosis and restenosis,, one of ordinary skill in the art would have been motivated to administer the PSGL-1 and fragments thereof, as taught by Cummings et al. in various vessel-occlusive techniques given its properties of inhibiting platelet-leukocyte interactions for various clinical applications, including atherosclerosis and ischemia, myocardial infarction and reperfusion injury, as taught by Cummings et al. with an expectation of success.

Also, note that Cummings et al. teach that the therapeutic use that reduce leukocyte adherence in ischemic myocardium can significantly enhance the therapy efficacy of thrombolytic agents (see column 18, paragraph 7).

Given that thrombolytic agents were standard practice in the treatment of atherosclerosis as well as the vessel-corrective techniques at the time the invention was made, the ordinary artisan would have administered PSGL taught by Cummings et al. into standard common therapeutic regimens to treat the same patients encompassed by the claimed methods in efforts to increase the efficacy of thrombolytic agents at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

In response to appellant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See In re Gorman, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Nothing of record would indicate that it would have been nonobvious to employ those teachings. That the teachings relied upon were repeated in a number of references, further strengthens the conclusion of obviousness. See Kansas Jack, Inc. V. Kuhn et al. 219 USPQ 857, 860 (Fed. Cir. 1983).

Appellant's arguments have not been found persuasive for the reasons of record.

Rebuttal: Wagner (I) 131 Declaration.

Appellant's Brief simply asserts that the Cummings et al. reference has been antedated as a result of the prior conception and subsequent reduction to practice of the claimed invention, coupled with the requisite diligence, as shown in the Wagner (I) 131 Declaration without more.

The following from the prosecution history with respect to the Wagner 131 Declaration is set forth herein.

Appellant's reliance on the 1.131 declaration under 37 C.F.R. 1.131, filed 3/18/03 (Exhibit) in conjunction with the Brief, have been fully considered but are not found convincing essentially for the reasons of record.

Appellant believes that the possession of the genus is sufficient to constitute possession of the species. Appellant has asserted their belief in that the 131 Declaration was adequate and sufficient to antedate the Cummings et al. Reference since the declaration shows that applicant was in possession of the genus which include the species of Cummings et al.

Appellant has asserted that the enclosed Declaration by the co-inventors demonstrates that the conception of the instant invention occurred as early as 1988 and that an actual reduction to practice occurred as early as 9/13/93. The time period between 11/16/92 and 9/13/93 was consumed by the development of a knockout mouse model for atherosclerosis and the testing of the mouse model to verify the inventive concept. It has been noted that the conclusion of the results of the experiment were collected and analyzed on or about 5/6/94.

This observation date of 5/6/94 is after the priority date of prior art Cummings et al. and Larsen et al. for example.

Appellant relies on the statement:

"Macrophages eat bits of activated platelets. ELAM-1 = Padgem. Do monocytes bind to Padgem on platelets. Padgem is an opsonizing agent to get rid of debris of platelets."

Appellant asserts their conception of a functional relationship between E-selectin and P-selectin, and that P-selectin mediates the binding of platelets to macrophages.

In addition, appellant has relied upon the preparing a P-selectin knock-out mouse to study the role of P-selectin in atherosclerosis by feeding the P-selectin deficient mice with a lipid diet. The results of this study demonstrate a reduction in the size of atherosclerotic lesions in P-selectin deficient mice.

While appellant has asserted that based upon these results that inhibitors of P-selectin/ligand binding and/or E-selectin/ligand binding would be useful for the treatment or inhibition of atherosclerosis, constituting an actual reduction to practice the claimed invention (e.g. see the last sentence of Section 8 of the Wagner 131 Declaration);

The 131 Declaration and Exhibits do not appear to provide objective evidence for this conclusion of inhibitors would be useful for the treatment or inhibition of atherosclerosis.

Also, as pointed out previously,

The 131 Declaration does not appear to indicate particular inhibitors for the claimed methods, and more pointedly, does not indicate the use of PSGL-1

The evidence, submitted is insufficient to establish a reduction to practice of the invention in this country prior to the effective date of the prior art.

The 37 CFR 1.131 declaration must establish possession of either the whole invention claimed or something falling within the claim in the sense that the claims as a whole reads on it. In re Tanczyn 146 USPQ 298 (CCPA 1965). See MPEP 715.02.

Appellant has not overcome the prior art rejection by showing that the differences between the claimed invention and the showing under 37 CFR 1.131 would have been obvious to one of ordinary skill in the art, in view of appellant's 37 CFR 1.131 evidence, prior to the effective date of the references(s) or the activity.

The test is whether the facts set out in the affidavit are such as would persuade one skilled in the art that the application possessed so much of the invention as is shown in the references. In re Schaub 190 USPQ 324 (CCPA 1976). See MPEP 715.03.

Appellant'ss evidence of conception and diligence does not address the critical elements of the instant claims which are drawn to a method of treating or inhibiting atherosclerosis, including treating atherosclerosis to a mammal to which a vessel-corrective technique is administered by administering PSGL-1 by administering repeatedly in sequential doses by the controlled release to the mammal over a period of months or years.

Other than appellant's assertions, there is insufficient objective evidence the ordinary artisan would have taken appellant's statement: "Macrophages eat bits of activated platelets. ELAM-1 = Padgem. Do monocytes bind to Padgem on platelets. Padgem is an opsonizing agent to get rid of debris of platelets." to establish possession of treating atherosclerosis in a mammal by administering PSGL-1 by administering repeatedly in sequential doses by the controlled release to the mammal over a period of months or years.

Similarly there is insufficient evidence the ordinary artisan would have taken applicant preparation of a P-selectin knock-out mouse to study the role of P-selectin in atherosclerosis by feeding the P-selectin deficient mice with a lipid diet to establish possession of treating atherosclerosis in a mammal by administering PSGL-1 repeatedly in sequential doses by the controlled release to the mammal over a period of months or years.

Further, it is noted that appellant's evidence relies upon experimental animals serves as model systems to selectively investigate different steps of the injury cascade providing specific insights into key mechanisms operating in diseases. While appellant's studies with a P-selectin knockout mouse may have provided insights into the role of P-selectin to atherosclerosis, there is insufficient evidence and correlation of establishing possession of treating atherosclerosis in a mammal by administering PSGL-1, particularly given the absence of any disclosure of administering PSGL-1 in appellant's 131 Declaration and Exhibits.

Again, appellant has not provided objective evidence that applicant was in possession of PSGL-1 itself as well as its use as a therapeutic agent in treating atherosclerosis prior to the disclosure of the prior art. Appellant's reliance on a generic concept of a possible role of P-selectin in atherosclerosis and subsequent findings in an experimental animal model does not support the use of PSGL-1 in treating atherosclerosis repeatedly in sequential doses by the controlled release to the mammal over a period of months or years.

In addition in responding to the prior art teachings of Cummings et al.,

the Brief (e.g. see page 5, paragraph 2) as well as the Wagner (II) 132 Declaration (e.g. see Section 2 of the 132 Declaration) indicates that it is appellant's position that there was no expectation of success that PSGL-1 could be used to reduce plaque formation and further that a long term treatment regime would be required to achieve this result.

Given the limited information relied upon by appellant in the 131 Declaration / Exhibits which do not identify PSGL-1, which do not identify or suggest PSGL-1 as an inhibitor of P-selectin mediated interactions, nor in the treatment of atherosclerosis and which does not indicate the criticality of long term therapeutic regimens would mention the use of PSGL-1,

a fair reading of appellant's position in the Brief and Wagner (II) 132 Declaration would indicate that appellant's 131 Declaration lack sufficient possession of certain critical elements of the claimed methods, namely the agent PSGL-1, the suggestion to use PSGL-1 in treating atherosclerosis and the need for long term treatment regimens to treat atherosclerotic patients.

It has been established that conception is more tha a mere vague idea of how to solve a problem; the means themselves and their interactions must be comprehended also.

See MPEP 715.07 III.

Absent a clear support or facts are establishing appellant's assertions of conception and diligence (and reduction to practice or subsequent reduction to practice) before the prior art, appellant's arguments are not found persuasive and the rejection is maintained for the reasons of record.

Appellant's arguments have not been found persuasive.

(11) For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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